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Development of a Mucoadhesive Sublingual Spray of Palonosetron Hydrochloride: A Patient-Friendly Approach to Chemotherapy-Induced Nausea and Vomiting

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) is a common complication of cancer therapy, and rapid-onset antiemetic drug delivery may improve therapeutic convenience. Palonosetron hydrochloride (PAL HCl), a potent 5-HT3 receptor antagonist with a prolonged half-life, was formulated as a mucoadhesive sublingual spray to facilitate rapid drug release and transmucosal permeation while reducing gastrointestinal exposure.

The spray formulations were prepared by a simple mixing method using trimethyl chitosan (TMC) as a mucoadhesive and permeation-enhancing polymer, with propylene glycol (PG) and PEG-400 as formulation variables. Nine formulations (F1–F9) were prepared using a 3^2 full factorial design and evaluated for physicochemical characteristics, spray performance, drug release, and ex-vivo permeation. The optimized formulation, F1, exhibited clear appearance, pH 6.2 ± 0.1, drug content of 99.4 ± 0.5%, viscosity of 20 ± 2 cP, uniform spray pattern, droplet size of 60 ± 2 µm, and mucoadhesion time of 90 ± 5 min. F1 showed 88.9% cumulative drug release at 10 min and 98.6% at 60 min.

The cumulative drug permeation of F1 was 79.6% at 60 min. In the ex-vivo permeation study, cumulative permeation increased from 42.96 ± 1.12% at 10 min to 81.45 ± 1.28% at 60 min. The findings demonstrate that the developed TMC-based PAL HCl sublingual spray exhibited satisfactory formulation characteristics, rapid drug release, and enhanced ex-vivo permeation.

Keywords: Antiemetic, PEG-400, diffusion, Spray, sublingual mucosa, Trimethyl-chitosan.

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1. Introduction:-

Chemotherapy-induced nausea and vomiting is a serious concern for cancer patients. About 54%–96% population are affected by CINV. The, effective treatment for CINV is extremely necessary for cancer patients. Improvement in antiemetic therapy could have potentially benefited surgical patients, particularly that undergoing outpatient surgery. 5-HT3 receptor antagonist has an antiemetic property which is primarily prescribed for treatment of nausea and vomiting. [1] Palonosetron Hydrochloride (Palonosetron HCl) is one of the potent 5-HT3 receptor antagonist with a binding affinity 100 times stronger and a significantly longer half-life (~ 40 h) than other agents in its class.[2] Palonosetron is marketed as tablet , injection and capsule. It is absorbed from GI tract. However, it has low bioavailability due to first pass effect. [3] So, one of the alternate route is Sublingual route which .means the drug put under the tongue means placed beneath the tongue this area consists blood vessels, and rapidly absorbed via blood vessel rather than via Digestive tract. [4] The approval of sublingual spray by the regulatory agencies may commence further research in this field by subsuming various essential drugs for indications such as cancer pain, cardiovascular issue etc. This study on the drawback of conventional sublingual drug delivery system and the approach by which these drawbacks can be overruled by spray technology in the sublingual area and the, in-depth mechanism of drug delivery through sublingual with the help of atomization followed by the entire formulation strategy along with evaluation and industrial perspective of the sublingual spray dosage form as a future tool of patient-friendly drug delivery. [5]

2. Method

2.1 Materials:-

Palonosetron hydrochloride (API) purchased from by Century Pharmaceuticals Ltd Vadodara. Excipients like Tri-methyl Chitosan (triveni interterm pvt ltd) , PEG-400 (BFC lab) propylene glycol (Star industry) use to enhance permeability of spray. Sodium citrate (Research lab) use to maintain the pH. Coloring agent and Menthol oil use as flavoring agent. Sodium benzoate use as preservative.

2.2 Preparation of sublingual spray formulation

Sublingual spray was mixed by simple mixing method Sublingual spray of palonosetron HCl was prepared by using simple mixing method First of all prepare a polymer complex of Api and TMC in 1:1 Ratio after then add propylene glycol,ethanol,PEG-400,Sodium benzoate ,sodium citrate, Sucralose mix well with glass road then make up the solution with the help of distilled water sonicate the solution 30-40min. (to mix well and clear the solution) and then filter the solution with the help of 0.45µ nylon filter, at end last menthol oil as flavoring agent. Fill the spray bottle above solution and label it. The formulation was optimized using DOE version 13.1 Full factorial design (3^2) and F1 to F9 batch was prepared in which F1 was best sublingual spray and optimized batch.

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Table no 1 Ingredients used in preparation of spray

Ingredient	Uses
Palonosetron Hydrochloride	API
Tri methyl Chitosan	Permeation enhancer
Sodium benzoate	Preservative
PEG-400	Stabilizer
Sodium Citrate	Buffering Agent
Propylene Glycol	Co solvent
Ethanol	Co solvent
Sucralose	Sweetener
Menthol oil	Flavoring agent
Purified Water	Solvent

2.3 Experimental work [23,24]**:-**

2.3.1 Physical Characteristic:- All the prepared formulation are visually inspected for color , clarity , visual dirt particles , precipitate formulation by the ingredient discoloration or cloudiness may indicate microbial contamination.

2.3.2 pH:- The pH of all the formulation is evaluated by use pH meter. The pH meter was set at neutral pH-7 in distal water by its adjusting screw and finally placed inside the solution and note the reading where the pH meter stops further fluctuation

2.3.3 Viscosity (cP):- Viscosity of the sample is determined by Oswald broke field viscometer by placing the 84 probe 64 of the instrument in the container containing the sample in appropriate quantity that the probe should get immersed in the sample to avoid error. Note the reading should be taken at which is constant repeat the process for as time and take mean viscosity

2.3.4 Drug content:- Assay of accurately weighed amount of formulation were carried out for the determination of net drug content. The weighed sample was dissolved in 10 ml of water distil and further it was filtered. The drug content was estimated Spectrophotometrically at 263 nm using standard curve

2.3.5 Spray Pattern:- Objective: To evaluate the uniformity and geometry of spray emitted from the formulation Materials: Sublingual spray bottle, Whatman filter paper sheet. Glass slide, methylene blue dye solution, Vernier calliper. Place a clean filter paper on a flat surface. Fix it properly to avoid movement. Add a small amount of water-soluble dye to the formulation for visibility. Hold the spray bottle at a fixed distance (5–10 cm) from the paper. Spray once

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(single actuation). Allow the sprayed pattern to dry at room temperature. Measure the diameter of the spray spot using a ruler or caliper. Observe the shape (circular, oval, irregular). Repeat perform the test 3 times and calculate mean ± SD. Spray pattern diameter (cm) Shape description

2.3.6 Droplet Size Analysis (µm):- Droplet size was determined using optical microscopy. The formulation was sprayed onto a glass slide and observed under a microscope. The diameter of droplets was measured, and the average droplet size was calculated. The below formulation shows a mean droplet size range of sublingual spray

Ideal Range (IMPORTANT) for sublingual spray: 10–100 µm

2.3.7 Muco adhesion Time: **-** Mucoadhesion time was determined using goat buccal mucosa mounted on a Franz diffusion cell. Fresh goat buccal mucosa was mounted on a glass slide, and the formulation was applied. The assembly was immersed in phosphate buffer (pH 6.8) at 37°C. The time required for complete detachment of the formulation was recorded as muco-adhesion time**.**

2.3.8 In Vitro Drug Release: **-** In vitro drug release study was carried out using a Franz diffusion cell. The dialysis membrane was mounted between donor and receptor compartments. Phosphate buffer (pH 6.8) was used as receptor medium and maintained at 37 ± 0.5°C with continuous stirring. A fixed amount of formulation was placed in the donor compartment. Samples were withdrawn at predetermined intervals and analyzed Spectrophotometrically at 263 nm. The cumulative percentage drug release was calculated**.**

2.3.9 Ex-vivo drug permeation study: - Ex vivo permeation study was performed using goat buccal mucosa mounted on a Franz diffusion cell. Samples were withdrawn at predetermined intervals (5, 10, 15, 30, 60, 120 min) and analyzed by using (263 nm) UV spectrophotometer Flux was calculated from the slope of cumulative drug permeation versus time plot.

3. Result

Palonosetron HCl sublingual spray formulations were prepared and filled in spray container was labelled F1 to F9. Each formulation was tested. Below table no 2 represents formulation composition and tested responses, % drug release and % drug permeation (60 min), % Drug Release (10 min) that were suitable for applying to the sublingual mucosal surface.

Table no 2 Test results of Palonosetron HCl spray formulation batches

INGREDIENT	F1	F2	F3	F4	F5	F6	F7	F8	F9
API+TMC (1:1)	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg
PG (ml)	5.0	5.0	5.0	3.5	3.5	3.5	4.25	4.25	4.25
PEG 400 (ml)	1.0	1.5	2.0	1.5	1.0	2.0	2.0	1.5	1.0
Ethanol (ml)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Sodium citrate (mg)	35	35	35	35	35	35	35	35	35
Sodium benzoate (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Menthol oil(ml)	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Water (ml)	qs to 15	qs to 15	qs to 15	qs to 15	qs to 15	qs to 15	qs to 15	qs to 15	qs to 15

3.1 Effect of selected variables on % Drug Release (10min) Y1

The surface plot demonstrated that % drug release at 10 min was influenced by the concentrations/volumes of PG and PEG-400. The response surface (Used DoE software version 13.1) showed an increasing trend in drug release with increasing PG levels. PEG-400 also contributed to the drug-release response, although its effect appeared comparatively less pronounced. The predicted drug-release response increased from approximately 65% in the lower-factor region to approximately 89% in the higher-response region.

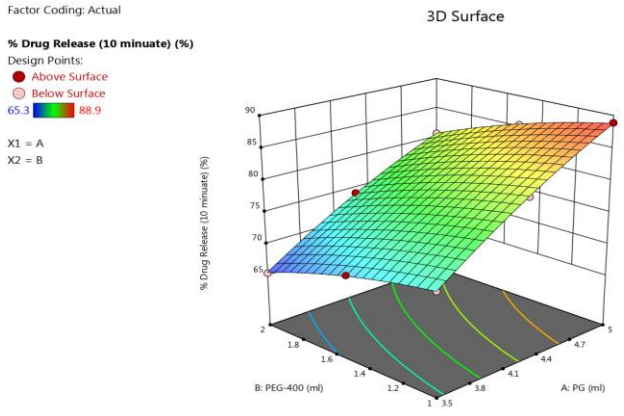


Figure no 1 Shows Effect of surface on PG (propylene glycol) and PEG-400 affect % drug release at 10 minutes

% Drug Release in (10 minute) = 78.6111 + 7.91667 * A + -3.76667 * B + -0.275 * AB + -1.01667 * A^2 + -0.766667 * B^2

The above equation coefficient is positive that means: increasing PG tends to increase drug release. And because its coefficient is relatively large, PG has a strong positive influence on the response.

3.2 Effect of selected variables on % drug permeation (60min) Y2:-

The surface plot demonstrated that PG and PEG-400 influenced the % drug permeation. (Used DoE software version 13.1) A pronounced increase in drug permeation was observed with increasing PG concentration, as indicated by the progressive rise of the response surface from the blue/green region toward the yellow/orange region. PG appeared to exert a greater influence on drug permeation than PEG-400, whereas PEG-400 showed a comparatively smaller effect. The highest predicted drug permeation was observed in the region of higher PG levels, reaching approximately 80%. Thus, the response-surface analysis suggests that PG plays an important role in enhancing the permeation of the drug through the selected membrane/model

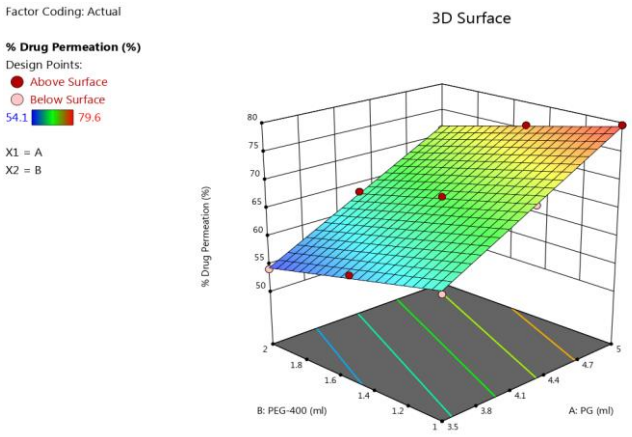


Figure no 2 Shows effects of surface graph represents the effect of PG and PEG-400 on % drug permeation**.** Here, the response is % drug permeation, rather than drug release.

% Drug Permeation = 28.1389 + 11.7333 * A + -7.43333 * B

The equation explained that PG is the main positive contributor to drug permeation, whereas increasing PEG-400 has a negative effect on the predicted permeation. It also indicated that PG

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has a comparatively stronger influence on drug permeation within the studied formulation range.

Table no 3 Evaluation parameters of formulation batches

Evaluation Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Appearance	CLEAR	clear	clear	clear	slightly turbid	clear	clear	clear	clear
pH	6.2±0.1	6.3±0.1	6.5±0.1	6.0±0.1	5.8 ±0.1	6.2±0.1	6.4±0.1	6.3±0.1	6.1±0.1
% Drug content	99.4±0.5	98 ±0.7	97±0.8	97.5 ±0.9	96.2±1.1	98.1 ±0.8	98.5 ±0.7	98.2±0.6	97.8 ±0.7
Viscosity (cP)	20 ±2	28 ±2	40 ±3	20 ±2	15 ±2	28 ±3	35±3	25 ±2	18 ±2
Spray pattern	UNIFORM	uniform	Thick spray	uniform	Slightly non uniform	uniform	Slightly thick	uniform	uniform
Droplet size (µm)	60 ±2	56 ±2	62 ±3	42 ±2	38 ±2	46 ±3	58±3	52 ±2	48 ±2
Mucoadhesion times	90 ±5	104 ±6	152 ±7	120 ±6	109 ±5	136 ±8	140±6	115 ±5	100 ±4

Above table shows the evaluation parameters of Palonosetron HCl sublingual spray formulation (F1-F9 batch) which were evaluated the appearance,pH viscosity, spray pattern, Droplet size ,Mucoadhesive time . All formulations were clear except F5, which exhibited slight turbidity. The pH values ranged from 5.8 ± 0.1 to 6.5 ± 0.1**,** indicating an appropriate pH range for sublingual administration. The percentage drug content was found to be within 96.2 ± 1.1% to 99.4 ± 0.5%**,** demonstrating good drug uniformity. Viscosity values ranged from 15 ± 2 to 40 ± 3 cP, which supported adequate spreadability of the formulations. Most formulations exhibited a uniform spray pattern, whereas F3 and F7 showed a slightly thick spray and F5 exhibited slight non-uniformity. The droplet size ranged from 38 ± 2 to 62 ± 3 µm. Mucoadhesion time varied from 90 ± 5 to 152 ± 7 min**,** with F3 showing the highest Mucoadhesion time. Among the formulations, F1 exhibited a clear appearance, pH of 6.2 ± 0.1, drug content of 99.4 ± 0.5%, viscosity of 20 ± 2 cP, uniform spray pattern, droplet size of 60 ± 2 µm, and Mucoadhesion time of 90 ± 5 min**.** The observed muco-adhesion time of 90 ± 5 min was considered adequate to provide sufficient residence at the sublingual mucosa while avoiding excessive polymer-mediated viscosity and prolonged adhesion. So, based on its overall physicochemical characteristics and satisfactory spray performance, F1 was selected as the optimized formulation.

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Table no 4 % Drug Release sublingual spray

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
10	88.9%	85.4%	80.7%	69.8%	72.4%	65.3%	74.2%	78.6%	81.5%
20	92.5%	89.2%	85.8%	75.6%	78.2%	70.5%	79.4%	83.1%	86.3%
30	95.1%	92%	88.6%	80.2%	82.5%	75.8%	83.2%	86.5%	89.4%
40	96.8%	94.1%	90.5%	83%	85.1%	78.6%	85.7%	88.9%	91.2%
50	97.9%	95.6%	92.1%	85.4%	87%	80.9%	87.5%	90.3%	92.6%
60	98.6%	96.7%	93.4%	86.8%	88.5%	82.3%	88.9%	91.5%	93.8%

Table no 5 % Drug permeation of sublingual spray

TIME(MIN)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
10	25.9 %	24.3%	21.5%	16.5%	18.5%	14.3%	18.1%	20.6%	22.4%
20	45.2%	40.1%	39.5%	30.2%	32.5%	28.6%	31.0%	35.4%	38.4%
30	60.5%	59.3%	55. %4	42. %7	45.8%	39.5%	43.2%	48.7%	52.4%
40	73.4%	68.7%	64.7%	52.1%	55.2%	49.6%	55.8%	60.4%	64.9%
50	76.8%	72.6%	69.2%	56.7%	59. %6	52.3%	60.3	65.3%	67.9%
60	79.6%	75.8%	71.3%	58.6%	61.8%	54.1%	63.5	67.2%	70.4%

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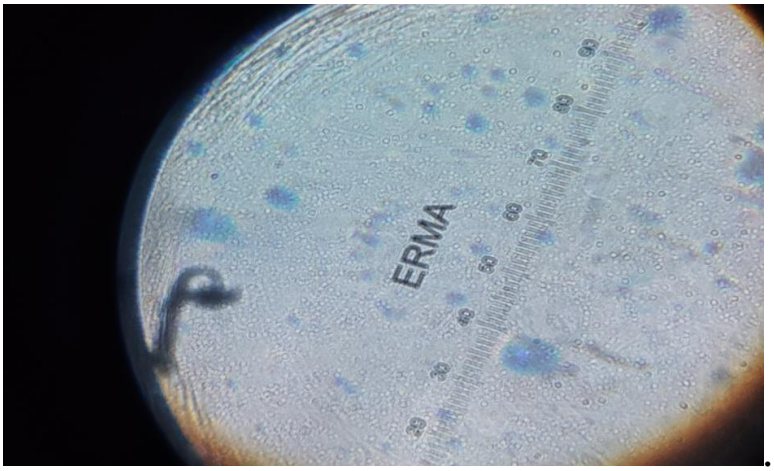


Figure no 3 Drop let size analysis

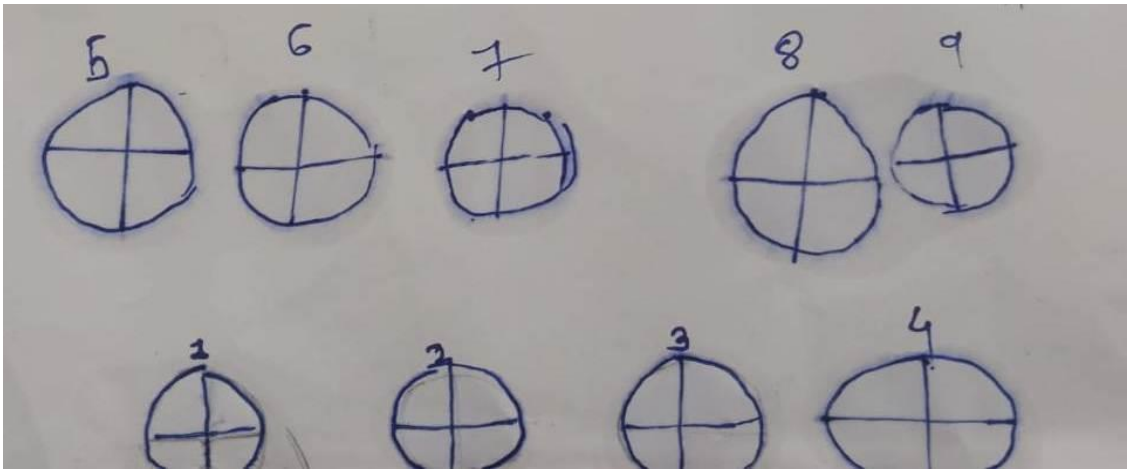


Figure no 4 Spray pattern analysis

3.3 Ex-vivo permeability test

Table no 6 *Ex-Vivo* permeation tests

Time (min)	Observed value
10	42.96% ±.1.12
20	64.85% ±.1.53
30	68.70% ±1.15
40	73.74% ±1.06
50	79.02% ±1.68
60	81.45% ±1.28

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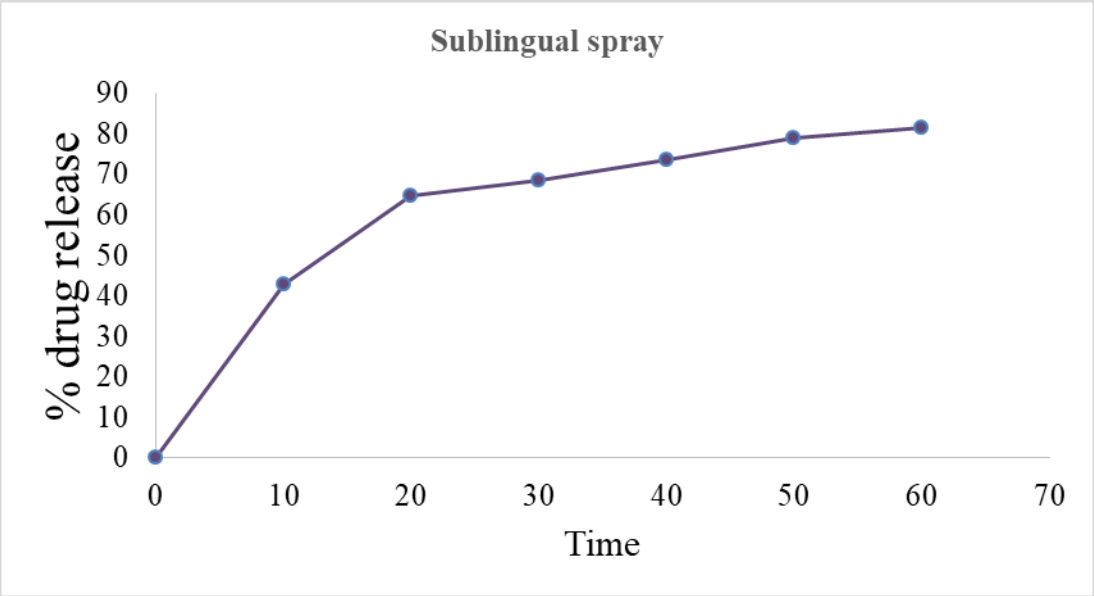


Figure no 5 *Ex-Vivo* permeation studies

4. Discussion

The present study was carried out to develop and optimize a Mucoadhesive sublingual spray of Palonosetron hydrochloride (PAL HCl) for rapid drug release and enhanced transmucosal permeation. The sublingual route provides a highly vascularised mucosal surface and can facilitate systemic drug absorption while avoiding gastrointestinal exposure and first-pass metabolism [11, 12]. However, continuous salivary secretion and swallowing may reduce the residence time of liquid formulations at the sublingual site. Mucoadhesive polymers can overcome this limitation by increasing the contact time between the formulation and mucosal surface [12, 13].

PAL HCl is freely soluble in water and soluble in propylene glycol [14]. In the present study, the solubility study performed in the present investigation further evaluated its solubility in pH 6.8 phosphate buffer. Therefore, the major formulation consideration was maintaining adequate drug availability at the mucosal surface and facilitating its permeation rather than simply improving drug solubility. Trimethyl Chitosan (TMC) was incorporated to improve mucosal interaction and residence time. TMC is a cationic Chitosan derivative capable of interacting with mucin and has been reported to possess mucosal permeation-enhancing properties [15, 16]. Thus, TMC may provide both mucoadhesive and permeation-enhancing effects in the developed spray.

Propylene glycol and PEG-400 were selected as formulation variables, and their effects were evaluated using % drug release at 10 min (Y1) and cumulative % drug permeation at 60 min (Y2). The drug-release model showed a positive effect of propylene glycol and a negative effect

of PEG-400. The positive effect of propylene glycol may be attributed to its ability to maintain PAL HCl in a dissolved state, whereas increasing PEG-400 may increase formulation viscosity and consequently retard drug diffusion [14].

The ex-vivo permeation study was conducted across the sublingual mucosal membrane for 60 min, with cumulative % drug permeation at 60 min selected as Y2**.** Propylene glycol showed a positive influence on cumulative permeation, whereas PEG-400 showed a negative influence. The enhanced permeation may be associated with improved drug availability at the mucosal surface together with the permeation-enhancing contribution of TMC [15, 16].

The prepared formulations exhibited acceptable physical appearance, pH, drug content, viscosity and other evaluated formulation characteristics. The formulations also demonstrated acceptable spray pattern, spray angle, droplet characteristics and device performance, indicating compatibility of the formulation with the selected spray device.

Based on simultaneous optimization of Y1 and Y2, F1 was selected as the optimized formulation. Overall, the findings suggest that the optimized TMC-based PAL HCl sublingual spray provided satisfactory formulation characteristics, rapid drug release and enhanced ex-vivo permeation, supporting its potential as a sublingual drug-delivery system.

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